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NOTIFICATION OF ELECTION

(PCT Rule 61.2)

To:

Assistant Commissioner for Patents
United States Patent and Trademark Office
Box PCT
Washington, D.C.20231
ETATS-UNIS D'AMERIQUE

in its capacity as elected Office

Date of mailing (day/month/year) 16 May 2000 (16.05.00)	
International application No. PCT/EP99/07765	**Applicant's or agent's file reference** KLP/B45160
International filing date (day/month/year) 08 October 1999 (08.10.99)	**Priority date** (day/month/year) 16 October 1998 (16.10.98)
Applicant D'HONDT, Erik	

1. The designated Office is hereby notified of its election made:

[X] in the demand filed with the International Preliminary Examining Authority on:

15 April 2000 (15.04.00)

[ ] in a notice effecting later election filed with the International Bureau on:

2. The election [X] was

[ ] was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

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Authorized officer

Juan Cruz

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
KLP/B45160		
International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/EP99/07765	08/10/1999	16/10/1998
International Patent Classification (IPC) or national classification and IPC C12N7/00		
Applicant SMITHKLINE BEECHAM BIOLOGICALS S.A. et al.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 6 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e. sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations suporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☒ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
15/04/2000	26.01.2001
Name and mailing address of the international preliminary examining authority: European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465	Authorized officer Armandola, E Telephone No. +49 89 2399 7493

Form PCT/IPEA/409 (cover sheet) (January 1994)

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No. PCT/EP99/07765

I. Basis of the r p rt

1. This report has been drawn on the basis of *(substitute sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to the report since they do not contain amendments (Rules 70.16 and 70.17).)*:
Description, pages:

1-18 as originally filed

Claims, No.:

1-16 as originally filed

Drawings, sheets:

1/4-4/4 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language: , which is:

- ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in written form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

- ☐ the description, pages:
- ☐ the claims, Nos.:

☐ the drawings, sheets:

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)):

   (Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.)

6. Additional observations, if necessary:

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	1-5, 10-15
	No:	Claims	6-9, 16
Inventive step (IS)	Yes:	Claims	
	No:	Claims	1-16
Industrial applicability (IA)	Yes:	Claims	1-16
	No:	Claims	

2. Citations and explanations
   see separate sheet

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the question whether the claims are fully supported by the description, are made:
see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Reference is made to the following documents:

D1:US-A-5 268 292 (MARGOLIS HAROLD S ET AL) 7 December 1993 (1993-12-07)

D2:BISHOP NAOMI E ET AL: 'Rapid and efficient purification of hepatitis A virus from cell culture.' JOURNAL OF VIROLOGICAL METHODS 1994, vol. 47, no. 1-2, 1994, pages 203-216, XP000891975 ISSN: 0166-0934

D3:WO 95 17209 A (SMITHKLINE BEECHAM BIOLOG ;MOMIN PATRICIA MARIE (BE); GARCON NATHA) 29 June 1995 (1995-06-29) cited in the application

D4:ANDRE F E ET AL: 'INACTIVATED CANDIDATE VACCINES FOR HEPATITIS A' PROGRESS IN MEDICAL VIROLOGY , vol. 37, 1990, pages 72-95, XP000904877 ISSN: 0079-645X cited in the application

Document D1 discloses the purification of Hepatitis A virus (HAV) by a method that comprises harvesting of virus from cell culture medium and cell lysates and treatment with trypsin to degrade cellular proteins. The virus preparation obtained is highly purified and cell protein contaminants cannot be detected in polyacrylamide gel electrophoresis.

Document D2 describes the rapid and efficient purification of HAV by a method that comprises a trypsin digestion step to separate the virus from cells. The method yields a pure preparation of virus that can be inactivated to prepare a vaccine.

Document D3 refers to vaccine compositions comprising an oil in water emulsion with 2 De-O-acylated monophosphoryl lipid A and QS21. The composition can be used to prepare an HAV vaccine by including HAV antigens.

Document D4 describes the preparation of a HAV vaccine by purification of HAV by ultrafiltration and chromatography, inactivation and absorption to alum which serves as an

adjuvant.

Novelty and inventive step (Art. 33(2) (3) PCT)

i) with regard to Claims 6-9 and 16 it should be noted that a known product cannot be considered novel just because it is produced by means of a new process. Therefore, Claims 6-9 and 16, directed to an inactivated HAV, cannot be considered novel in view of document D4, which discloses inactivated HAV, a method for its preparation (p.75, 2. Purification and 3. Inactivation) and a vaccine comprising it (p.76, 4. Adsorption to Alum).

ii) Claims 1-5 can be considered novel because a process for the production of inactivated HAV encompassing precisely the steps listed in the claims has not been described in the available prior art. The claims cannot, however, be considered inventive.
The prior art discloses several methods to purify HAV (see D1, D2, D4). Document D1 discloses a purification method of HAV which includes a treatment with trypsin (D1, column 5, lines 57-59) and produces a virus preparation lacking cellular protein contaminants (Fig. 2B).
The subject-matter of Claim 1 differs from the disclosure of D1 in that in D1 the virus is not inactivated. D2 and D4, however, disclose the inactivation of a purified HAV preparation for the purpose of vaccination.
The skilled person wanting to prepare HAV for inclosure in a vaccine, would combine D1 and either D2 or D4 to add to the method of D1 the further step of inactivating the virus without the need to exercise inventive skills.
The additional chromatographic steps included in Claims 4 and 5 do not add an element of inventivity, because the skilled person would be aware of the need to separate impurities from the virus preparation and chromatography represents a classical methodology for this purpose (see also D4, p.75, 2. Purification).

iii) Claims 10-15 can be considered novel because a vaccine containing inactivated purified HAV and the adjuvants listed in the claims was not disclosed in the available prior art. The claims cannot, however, be considered inventive. D3 discloses vaccine compositions containing monophosphoryl lipid A, QS21 and an oil and tocopherol in an emulsion as adjuvant. Among the immunogens that can be part of the composition, HAV antigens are listed in D3.

The skilled person preparing a vaccine with HAV would find in D3 the hint that monophosphoryl lipid A and QS21 are suitable adjuvants for such a purpose and would apply this teaching without needing to exercise inventive skills.
The combination of different antigens to provide a multivalent vaccine can also not be regarded as inventive as it is a common practice in the vaccine field.

Re Item VIII
Certain observations on the international application

In Claim 11 the term "derivative" without other specifications renders the claim unclear because the skilled person would not know the technical features that should or may characterize this derivative.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(51) International Patent Classification 7 :
C12N 7/00, A61K 39/29, 39/295, A61P 31/12

A2

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(22) International Filing Date: 8 October 1999 (08.10.99)

(30) Priority Data:
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(71) Applicant *(for all designated States except US)*: SMITHKLINE BEECHAM BIOLOGICALS S.A. [BE/BE]; Rue de l'Institut 89, B–1330 Rixensart (BE).

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(74) Agent: PRIVETT, Kathryn, Louise; SmithKline Beecham, Corporate Intellectual Property, Two New Horizons Court, Brentford, Middlesex TW8 9EP (GB).

(81) Designated States: CA, JP, US, European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE).

Published
Without international search report and to be republished upon receipt of that report.

(54) Title: HEPATITIS A VACCINES

(57) Abstract

A process for the production of inactivated Hepatitis A virus substantially free of host cell contamination is described, the process comprising: a) culturing Hepatitis A virus and harvesting a hepatitis A preparation; b) treating said hepatitis A preparation with a protease; and thereafter c) separating intact virus from protease–digested material; d) inactivating said virus. Also described are vaccines comprising the inactivated hepatitis A virus, preferably in combination with strong adjuvants.

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INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

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